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## Adsorption of Nonionic Surfactants on Sulfathiazole and Naphthalene and Flocculation-Deflocculation Behavior of These Suspensions

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**Abstract** □ The adsorption of polyoxyethylated nonyl-phenols and octyl-phenols, having different polyoxyethylene chain lengths, on sulfathiazole and naphthalene was studied. Adsorption isotherms for these surfactants on sulfathiazole are S-shaped, and the adsorption amounts at saturation were greater than those for the closest packing at the air-solution interface. These results suggest that some multilayer adsorption or aggregate formation on the surface of solid occurred above a certain concentration. In the case of naphthalene, all isotherms are of the Langmuir type and the areas per molecule calculated from the saturation adsorption were found to be considerably larger than the values for the air-solution interface. It is likely that the hydrocarbon chains adhere to the surface of naphthalene, lying flat, while the polyoxyethylene chains are directed toward the solution. Flocculation-deflocculation measurements for both systems were carried out by the sedimentation volume method, and the results support the adsorption mechanisms described.

**Keyphrases** □ Polyoxyethylated octyl- and nonyl-phenols—adsorption on sulfathiazole and naphthalene, flocculation-deflocculation behavior of suspensions □ Surfactants, nonionic—adsorption on sulfathiazole and naphthalene, flocculation-deflocculation behavior of suspensions □ Adsorption of polyoxyethylated octyl- and nonyl-phenols on sulfathiazole and naphthalene—adsorption isotherms, flocculation-deflocculation behavior □ Sulfathiazole—adsorption behavior of polyoxyethylated octyl- and nonyl-phenols □ Naphthalene—adsorption behavior of polyoxyethylated octyl- and nonyl-phenols □ Flocculation-deflocculation behavior—suspensions of polyoxyethylated octyl- or nonyl-phenols and sulfathiazole or naphthalene

Many surfactants are capable of affecting the state of dispersion of powder particles in suspension. To examine the mechanism of action of surfactants in flocculation-deflocculation phenomena, it is desirable to investigate the adsorption of surfactants on powders. Several workers have studied the adsorption behavior and/or the dispersing action of nonionic surfactants. The adsorption of polyoxyethylated alkyl-phenols on sand and of ethylene oxide-propylene oxide condensates on quartz has been reported (1, 2). Kuno and

Abe (3) reported the adsorption of polyoxyethylated nonyl-phenols on calcium carbonate and carbon black from both aqueous and cyclohexane solutions. The adsorption of nonionic surfactants by textile fibers was studied by Weatherburn and Bayley (4), Nemoto and Miwa (5), and Schott (6).

Corkill *et al.* (7) studied the adsorption of polyoxyethylene glycol monoalkyl ethers on graphon at different temperatures and obtained the adsorption isotherms. They also measured the heats of adsorption calorimetrically. Other investigators (8, 9) commented on the influence of the adsorption of polyoxyethylene glycol monoalkyl ethers on the stability of silver iodide and polystyrene latex sols. In most of these studies, the adsorbents examined were inorganic compounds or polymers. Only a few workers have performed this kind of study using pharmaceutical or organic powders. The adsorption of polyoxyethylated nonyl-phenol on sulfamines (10) and of several nonionic surfactants on griseofulvin (11) has been reported.

The purpose of this work was to investigate the adsorption of nonionic surfactants on some organic powders and to find a certain relation between the flocculation-deflocculation behavior of these suspensions and the adsorption results. The surfactants used were polyoxyethylated nonyl-phenols and octyl-phenols. Sulfathiazole (polar compound) and naphthalene (nonpolar) were selected as adsorbents.

#### EXPERIMENTAL

**Materials**—Series of polyoxyethylated nonyl-phenols and octyl-phenols were prepared by repeated distillation of commercial products<sup>1</sup>. The average polyoxyethylene chain lengths were determined from their hydroxyl values. Table I gives the CMC and

<sup>1</sup> Nippon Nyukazai Co. Ltd., Tokyo, Japan.

**Table I—CMC and Close-Packed Areas at the Air-Solution Interface for the Surfactants Used**

Surfactant	CMC $\times 10^4$ moles/l.	Area per Molecule at Air-Solution Interface, $\text{Å}^2$
Polyoxyethylated nonyl-phenol-5.8 <sup>a</sup>	0.25	39
Polyoxyethylated nonyl-phenol-6.6	0.4	44
Polyoxyethylated nonyl-phenol-8.5	0.4	53
Polyoxyethylated nonyl-phenol-9.8	0.6	61
Polyoxyethylated nonyl-phenol-11.7	0.8	62
Polyoxyethylated octyl-phenol-7.7	2.7	59
Polyoxyethylated octyl-phenol-9.7	3.4	65

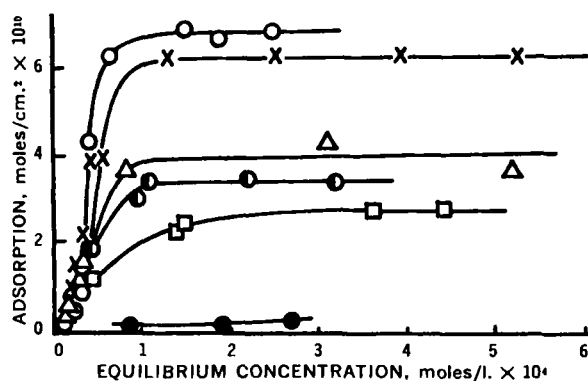
<sup>a</sup> Numbers indicate the average polyoxyethylene chain length.

average cross-sectional areas per molecule at the air-solution interface obtained from the data of surface tension using a tensiometer<sup>2</sup>. These values are in fair agreement with those in the literature (3, 12, 13).

Sulfathiazole<sup>3</sup> (JP VII) was finely ground and dried before use. Naphthalene was recrystallized from ethanol and then ground. The specific area for sulfathiazole was determined by the Brunauer-Emmett-Teller method with nitrogen adsorption and by gas-phase<sup>4</sup> and liquid-phase permeametry (14) to give 0.50 m.<sup>2</sup>/g. for sulfathiazole-A and 0.46 m.<sup>2</sup>/g. for sulfathiazole-B. Neither the nitrogen adsorption method nor gas-phase permeametry was applicable to naphthalene because the reproducibility of the data was poor. The value obtained by liquid-phase permeametry was 0.34 m.<sup>2</sup>/g.

**Procedure**—To 2.5 g. sulfathiazole or 5.0 g. naphthalene in a stoppered flask was added 50 ml. of surfactant solution. The flasks were shaken in water bath at 25° for 24 hr., after which the suspensions were centrifuged quickly. The equilibrium concentration for the supernate was determined by the cobalt blue method (15). The amount of surfactant adsorbed was calculated from the difference in the concentrations before and after adsorption.

The flocculation-deflocculation characteristics of suspensions were evaluated by the sedimentation volume method. A 2.5-g. sample of the test powder and 50 ml. of surfactant solution were

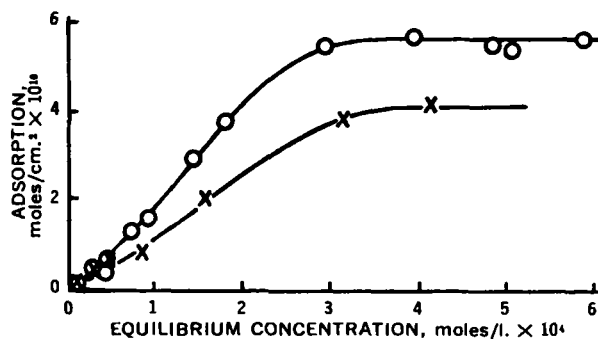


**Figure 1—Adsorption isotherms for polyoxyethylated nonyl-phenols and polyoxyethylene glycol 400 on sulfathiazole. Key (average polyoxyethylene chain lengths of polyoxyethylated nonyl-phenol): O, 5.8; X, 6.6; Δ, 8.5; ●, 9.8; □, 11.7; and ●, polyoxyethylene glycol 400.**

<sup>2</sup> DuNouy.

<sup>3</sup> Sankyo Co. Ltd., Tokyo, Japan.

<sup>4</sup> The instrument was prepared by Shimazu Seisakusho Ltd., Kyoto, Japan.



**Figure 2—Adsorption isotherms for polyoxyethylated octyl-phenols on sulfathiazole. Key (average polyoxyethylene chain length of polyoxyethylated octyl-phenol): O, 7.7; and X, 9.7.**

placed in a graduated test tube, which was shaken at 25° for 24 hr. and subsequently allowed to stand for an hour; the sedimentation volume was then measured. There was no appreciable change in the general tendency of the sedimentation volume even after standing overnight.

## RESULTS AND DISCUSSION

Figures 1 and 2 show the adsorption isotherms of polyoxyethylated nonyl-phenols and octyl-phenols on sulfathiazole, respectively. All isotherms are nearly S-shaped; i.e., the amount of adsorption is found to be less in the low concentration region and rises rapidly as the concentration increases, and then a plateau is reached at a concentration slightly above the CMC in solution.

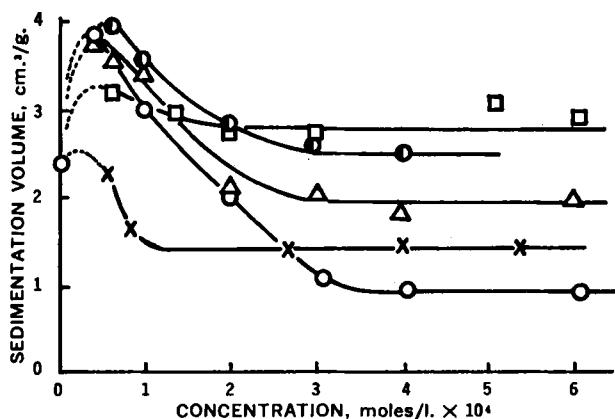
Nakagaki *et al.* (10) reported the adsorption of polyoxyethylated nonyl-phenol on sulfamines, but the adsorption behavior at low concentrations of the surfactant remains unanalyzed. Kuno and Abe (3) demonstrated that the adsorption isotherms of polyoxyethylated nonyl-phenols, having five to six ethylene oxide units, on calcium carbonate from aqueous solution are S-shaped and that the areas per molecule calculated from the saturation adsorption are smaller than the values obtained at the air-solution interface. They considered that the adsorbed surfactant is not in the state of individual molecules but is in the state of micelles. However, as Mathai and Ottewill (9) pointed out, it may be misleading to assume that the aggregate on the solid-solution interface has the same form as the micelles in bulk solution. Somasundaran *et al.* (16, 17) found that the adsorption of ionic surfactants on quartz and alumina increased markedly at a certain critical concentration less than that required for the micelle formation in the bulk solution. These workers concluded that this abrupt change in adsorption is due to the association of adsorbed surfactant ions to form two-dimensional aggregates or "hemimicelles" at the solid-solution interface.

The areas per molecule obtained from the saturation adsorption of polyoxyethylated nonyl-phenols and octyl-phenols on sulfathiazole are listed in Table II. From these values and the shape of the

**Table II—Areas per Molecule at the Solid-Solution Interface Calculated from the Saturation Adsorption**

Surfactant	Area per Molecule, $\text{Å}^2$ , Solid Sulfathiazole	Naphthalene
Polyoxyethylated nonyl-phenol-5.8 <sup>a</sup>	24	110
Polyoxyethylated nonyl-phenol-6.6	26	110
Polyoxyethylated nonyl-phenol-8.5	42	120
Polyoxyethylated nonyl-phenol-9.8	48	120
Polyoxyethylated nonyl-phenol-11.7	60	130
Polyoxyethylated octyl-phenol-7.7	29	180
Polyoxyethylated octyl-phenol-9.7	40	280

<sup>a</sup> Numbers indicate the average polyoxyethylene chain length.

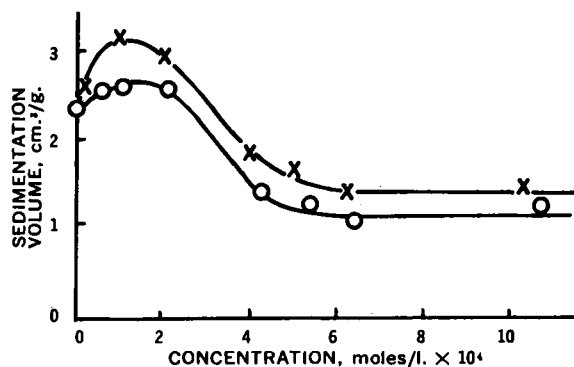


**Figure 3**—Sedimentation volume of sulfathiazole in the presence of polyoxyethylated nonyl-phenols. Key (average polyoxyethylene chain length of polyoxyethylated nonyl-phenol): O, 5.8; X, 6.6; Δ, 8.5; ●, 9.8; and □, 11.7.

adsorption isotherms, it is apparent that some multilayer adsorption or aggregate formation occurs on the surface above a certain concentration.

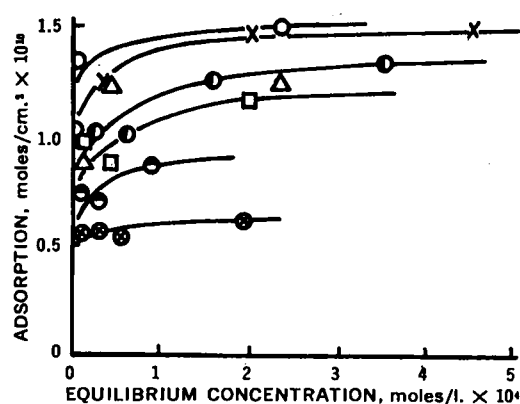
Flocculation-deflocculation measurements should be useful in the study of the behavior of surfactants at the solid-solution interface. Figures 3 and 4 show the sedimentation volume for sulfathiazole in the presence of polyoxyethylated nonyl-phenols and octyl-phenols, respectively. It is well known that, in coarse suspensions, completely deflocculated particles give a small sedimentation volume as they settle and flocculated ones tend to form a loose structure of large volume. In all cases in the present experiments, the sedimentation volume was large in the very low concentration region and fell gradually as concentration increased. Furthermore, maximum ease of transfer from the aqueous to the benzene phase was found at the concentration where a maximum in the sedimentation volume was observed. It seems likely, therefore, that initially surfactant molecules are adsorbed nearly flat with polyoxyethylene chains attached to the surface of sulfathiazole, which renders the surface more or less hydrophobic. With an increase in concentration, the surface aggregation of the surfactant molecules will be initiated before a close-packed monolayer of vertically orientated molecules is completed. Since most of the polyoxyethylene chains in such aggregates are supposed to be exposed to the aqueous phase, the surface of sulfathiazole will become hydrophilic.

The contribution of polyoxyethylene chain length to the adsorption of the surfactants on sulfathiazole is remarkable. Table II indicates that the degree of close-packing of molecules at the saturation adsorption becomes greater as the polyoxyethylene chain length decreases. This is in accordance with the works of Corkill *et al.* (7) and Elworthy and Guthrie (11). In the case of polyoxyethylated nonyl-phenol-11.7<sup>a</sup>, the area per molecule at the solid-solution



**Figure 4**—Sedimentation volume of sulfathiazole in the presence of polyoxyethylated octyl-phenols. Key (average polyoxyethylene chain length of polyoxyethylated octyl-phenol): O, 7.7; and X, 9.7.

<sup>a</sup> Number indicates the average polyoxyethylene chain length.



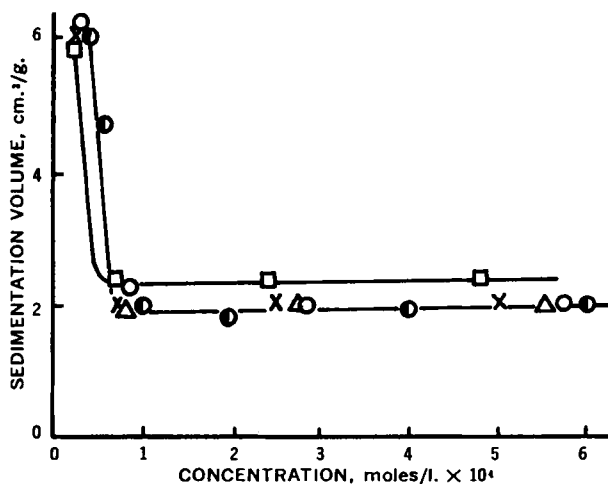
**Figure 5**—Adsorption isotherms for polyoxyethylated nonyl-phenols (A) and octyl-phenols (B) on naphthalene. Key (A—average polyoxyethylene chain length of polyoxyethylated nonyl-phenol): O, 5.8; X, 6.6; Δ, 8.5; ●, 9.8; and □, 11.7. Key (B—average polyoxyethylene chain length of polyoxyethylated octyl-phenol): ●, 7.7; and ○, 9.7.

interface is rather close to the value at the air-solution interface, so that it is possible to assume a close-packed monolayer. But it would be more reasonable to assume that some aggregate formation also occurs at the surface of the solid, although the tendency is less than in the cases of the surfactants containing shorter polyoxyethylene chains.

The results of the sedimentation volume measurements in the high concentration region simply reflect the adsorption results; *i.e.*, the sedimentation volume decreases with a decrease in polyoxyethylene chain length. On the other hand, at low concentrations, there seems to be no simple correlation between the sedimentation volume and the polyoxyethylene chain length. This may be due to the following two effects which counteract each other: (a) the smaller the hydrophilic group, the higher the magnitude of surface aggregate formation, and (b) the larger the hydrophilic group, the greater the steric stabilization against flocculation.

Although there was no essential difference between polyoxyethylated nonyl-phenols and octyl-phenols in the adsorption behavior onto sulfathiazole, the adsorption rise for polyoxyethylated octyl-phenols with an increase in concentration was slower than that for polyoxyethylated nonyl-phenols. This would be consistent with the fact that the values of the CMC for polyoxyethylated octyl-phenols are much larger than those of nonyl-phenols. Reflecting the adsorption results, the deflocculating action of polyoxyethylated octyl-phenols on sulfathiazole occurs at higher concentrations compared with polyoxyethylated nonyl-phenols.

The adsorption behavior and the deflocculating action of the surfactants on naphthalene seem to be simple, unlike sulfathiazole.



**Figure 6**—Sedimentation volume of naphthalene in the presence of polyoxyethylated nonyl-phenols. Key (average polyoxyethylene chain length of polyoxyethylated nonyl-phenol): O, 5.8; X, 6.6; Δ, 8.5; ●, 9.8; and □, 11.7.

As shown in Fig. 5, all isotherms are of the Langmuir type. Each curve starts from the origin and the amount adsorbed reaches a saturation value at or close to the CMC in solution. The areas per molecule calculated from the saturation adsorption were considerably larger than the values for the air-solution interface and were also larger than the dimensions of the hydrocarbon part of the molecule given by a molecular model. With an increasing polyoxyethylene chain length, the value of saturation adsorption decreases, but this trend is not so evident as compared with sulfathiazole.

Figure 6 presents the sedimentation volume of naphthalene in the presence of polyoxyethylated nonyl-phenols. At very low concentrations, naphthalene was only slightly wet by water and some portions of it floated, so measurement of the sedimentation volume was difficult. The sedimentation volume rapidly decreased with an increase in concentration and a highly deflocculated state was reached. The deflocculating action of the surfactants was not so influenced by the polyoxyethylene chain length.

It is likely, therefore, that the hydrocarbon chains of the surfactant molecules adhere to the surface of naphthalene and are lying flat, while the polyoxyethylene chains are directed toward solution.

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## GLC Determination of Nitroglycerin and Isosorbide Dinitrate in Human Plasma

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**Abstract** □ A procedure is described for the identification and quantitative determination of nitroglycerin and isosorbide dinitrate in plasma. The nitrates are extracted from plasma with ethyl acetate and measured by GLC with electron-capture detection. Quantitation is done using an internal standard. The lower limit of sensitivity for both substances is around 0.5 ng./ml. Results obtained with this method in humans are given.

**Keyphrases** □ Nitroglycerin—identification, GLC—electron-capture analysis, human plasma □ Isosorbide dinitrate—identification, GLC—electron-capture analysis, human plasma □ GLC—electron-capture detection—identification, analysis, nitroglycerin and isosorbide dinitrate in human plasma

Knowledge of the metabolic fate of the antianginal organic nitrates in man is hampered by a lack of sensitive analytical methods; attempts to measure plasma levels in man by colorimetric methods after administration of these nitrates were clearly unsuccessful (1, 2). The use of labeled substances has allowed the detection of small amounts of pentaerythritol tetranitrate in man (3, 4); for nitroglycerin and isosorbide dinitrate, the labeled compounds have been used in animals only (5-8).

The present authors previously described a GC method for the separation and identification of different organic nitrates in the nanogram range, using electron-capture detection (9). Only incomplete data about electron-capture detection for assay of organic nitrates in biological material have been published (10).

This report describes the use of GLC for the identification and quantitation of nitroglycerin and isosorbide dinitrate in plasma after administration of therapeutic doses in man.

#### EXPERIMENTAL

**Reagents**—Benzene<sup>1</sup>, trimethylchlorosilane<sup>2</sup>, and activated charcoal<sup>3</sup> filters were used. Ethyl acetate<sup>1</sup> was shaken three times with 10% ferrous sulfate and two times with water distilled in glass, stored over calcium chloride (95% minimum)<sup>2</sup>, and distilled immediately before use. Anhydrous sodium sulfate<sup>2</sup> was washed with ethyl acetate and dried at 100° for several hours. Nitroglycerin was available as a 1% solution in ethanol<sup>2</sup>, and isosorbide

<sup>1</sup> RS per pesticidi, Carlo Erba, Italy.

<sup>2</sup> Merck, Germany.

<sup>3</sup> Norite, Selecta n° 508, φ 4 cm., Schleicher & Schüll, Dassel, Germany.